Web Material

Temporal Relationship Between Uric Acid Concentration and Risk of Diabetes in a Community-based Study Population

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Web Table 1. Adjusted* hazard ratios (and 95% confidence intervals) for incident diabetes by quartile of uric acid concentration in strata of fasting glucose, insulin, or HOMA-IR level at baseline

Visit-based Diabetes (9 Years of Follow-up)	Quartile of Uric Acid Concentration (mg/dL)				
	0.5–4.9	5.0–5.8	5.9–6.9	7.0–15.9	*P*-trend†
Fasting glucose (mg/dL)					
<100	1.00 (reference)	0.65 (0.44, 0.97)	0.87 (0.60, 1.27)	0.94 (0.61, 1.46)	0.79
100–125	1.00 (reference)	1.10 (0.86, 1.41)	1.43 (1.13, 1.82)	1.54 (1.20, 1.98)	<0.001
Fasting insulin (μU/mL)					
<15	1.00 (reference)	0.93 (0.72, 1.21)	1.42 (1.11, 1.82)	1.63 (1.24, 2.15)	<0.001
≥15	1.00 (reference)	1.12 (0.77, 1.63)	1.20 (0.84, 1.71)	1.33 (0.93, 1.91)	0.07
HOMA-IR					
<2.6	1.00 (reference)	0.99 (0.71, 1.38)	1.40 (1.01, 1.95)	2.02 (1.40, 2.92)	<0.001
≥2.6	1.00 (reference)	0.95 (0.73, 1.25)	1.17 (0.91, 1.51)	1.24 (0.95, 1.62)	0.02

Abbreviation: HOMA-IR, homeostasis model assessment insulin resistance index.

*Adjusted for age, sex, race/study center, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, body mass index, estimated glomerular filtration rate, hypertension, parental family history of diabetes, education, smoking status, alcohol use, and diuretic use.

†*P*-trend was calculated using the median of each quartile as an ordinal variable.

Web Table 2. Visit 4 uric acid concentration or within-person change in uric acid concentration by duration of diabetes excluding participants using gout medications (*n* = 1,449)

	Mean Uric Acid Concentration (mg/dL) (95% CI)		
	Model 1	Model 2	Model 3
Category of diabetes duration			
0.0–4.3 years	Ref = 0	Ref = 0	Ref = 0
4.4–7.2 years	-0.28 (-0.49, -0.07)	-0.14 (-0.33, 0.04)	-0.07 (-0.25, 0.11)
7.3–9.0 years	-0.59 (-0.79, -0.39)	-0.38 (-0.56, -0.21)	-0.17 (-0.35, 0.01)
9.1–65.0 years	-0.56 (-0.78, -0.33)	-0.52 (-0.72, -0.32)	-0.29 (-0.49, -0.08)
P-trend	<0.001	<0.001	0.005
Uric acid concentration per 5 years with diabetes	-0.16 (-0.22, -0.10)	-0.15 (-0.21, -0.10)	-0.10 (-0.15, -0.05)

	Mean 9-year Within-person Change in Uric Acid (mg/dL) (95% CI)		
	Model 1	Model 2	Model 3
Category of diabetes duration			
0.0–4.3 years	Ref = 0	Ref = 0	Ref = 0
4.4–7.2 years	-0.45 (-0.65, -0.24)	-0.39 (-0.59, -0.19)	-0.33 (-0.52, -0.13)
7.3–9.0 years	-0.75 (-0.95, -0.55)	-0.67 (-0.86, -0.48)	-0.46 (-0.66, -0.27)
9.1–65.0 years	-0.15 (-0.37, 0.07)	-0.18 (-0.40, 0.04)	0.05 (-0.17, 0.28)
P-trend	0.04	0.02	0.90
Mean 9-year change per 5 years with diabetes	-0.01 (-0.02, 0.01)	-0.01 (-0.02, 0.00)	-0.03 (-0.09, 0.03)

Note: This analysis was conducted in visit 4 participants with a diagnosis of diabetes by visit 4.

Abbreviation: CI, confidence interval.

Model 1: Results adjusted for age, sex, race/study center.

Model 2: Results adjusted for Model 1 + low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, body mass index, estimated glomerular filtration rate, hypertension, parental family history of diabetes, education, smoking status, alcohol use, diuretic use.

Model 3: Results adjusted for Model 2 + fasting glucose + fasting insulin.

Web Table 3. Visit 4 uric acid concentration or within-person change in uric acid concentration by duration of diabetes excluding participants using insulin-based medications (*n* = 1,333)

Visit 4 Uric Acid	Mean Uric Acid Concentration (mg/dL) (95% CI)		
	Model 1	Model 2	Model 3
Category of diabetes duration			
0.0–4.3 years	Ref = 0	Ref = 0	Ref = 0
4.4–7.2 years	-0.30 (-0.51, -0.10)	-0.16 (-0.35, 0.02)	-0.08 (-0.26, 0.11)
7.3–9.0 years	-0.59 (-0.79, -0.39)	-0.39 (-0.57, -0.20)	-0.13 (-0.32, 0.05)
9.1–65.0 years	-0.63 (-0.89, -0.36)	-0.47 (-0.71, -0.22)	-0.16 (-0.41, 0.08)
P-trend	<0.001	<0.001	0.13
Uric acid concentration per 5 year with diabetes	-0.21 (-0.28, -0.13)	-0.17 (-0.23, -0.10)	-0.09 (-0.15, -0.02)

Within-person Change in Uric Acid (Visit 4 minus Visit 1)	Mean 9-year Within-person Change in Uric Acid (mg/dL) (95% CI)		
	Model 1	Model 1	Model 1
Category of diabetes duration			
0.0–4.3 years	Ref = 0	Ref = 0	Ref = 0
4.4–7.2 years	-0.43 (-0.64, -0.23)	-0.39 (-0.60, -0.18)	-0.33 (-0.53, -0.13)
7.3–9.0 years	-0.71 (-0.91, -0.51)	-0.64 (-0.85, -0.44)	-0.43 (-0.64, -0.22)
9.1–65.0 years	-0.23 (-0.50, 0.04)	-0.20 (-0.46, 0.07)	0.05 (-0.22, 0.32)
P-trend	<0.001	0.002	0.45
Uric acid concentration per 5 year with diabetes	-0.15 (-0.22, -0.07)	-0.14 (-0.22, -0.06)	-0.07 (-0.15, 0.00)

Note: This analysis was conducted in visit 4 participants with a diagnosis of diabetes by visit 4.

Abbreviation: CI, confidence interval.

Model 1: Results adjusted for age, sex, race/study center.

Model 2: Results adjusted for Model 1 + low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, body mass index, estimated glomerular filtration rate, hypertension, parental family history of diabetes, education, smoking status, alcohol use, diuretic use.

Model 3: Results adjusted for Model 2 + fasting glucose + fasting insulin.

Web Table 4. Visit 4 uric acid or within person change in uric acid concentration by duration of diabetes excluding participants using any diabetes medication, N = 860

	Mean Uric Acid Concentration (mg/dL) (95% CI)		
	Model 1	**Model 2**	**Model 3**
Category of diabetes duration			
0.0–4.3 years	Ref = 0	Ref = 0	Ref = 0
4.4–7.2 years	-0.27 (-0.50, -0.05)	-0.14 (-0.34, 0.07)	-0.07 (-0.27, 0.14)
7.3–9.0 years	-0.56 (-0.81, -0.31)	-0.33 (-0.57, -0.10)	-0.12 (-0.36, 0.12)
9.1–65.0 years	-0.77 (-1.26, -0.27)	-0.40 (-0.86, 0.06)	-0.32 (-0.77, 0.14)
P-trend	<0.001	0.004	0.14
Uric acid concentration per 5 year with diabetes	-0.33 (-0.45, -0.21)	-0.19 (-0.31, -0.08)	-0.13 (-0.25, -0.02)

	Mean 9-year Within-person Change in Uric Acid (mg/dL) (95% CI)		
	Model 1	**Model 2**	**Model 3**
Category of diabetes duration			
0.0–4.3 years	Ref = 0	Ref = 0	Ref = 0
4.4–7.2 years	-0.34 (-0.57, -0.11)	-0.27 (-0.50, -0.05)	-0.22 (-0.44, 0.00)
7.3–9.0 years	-0.63 (-0.88, -0.37)	-0.55 (-0.80, -0.29)	-0.34 (-0.60, -0.07)
9.1–65.0 years	-0.29 (-0.80, 0.21)	-0.22 (-0.73, 0.29)	-0.17 (-0.67, 0.33)
P-trend	<0.001	0.001	0.03
Mean 9-year change per 5 years with diabetes	-0.27 (-0.39, -0.15)	-0.24 (-0.37, -0.12)	-0.19 (-0.31, -0.06)

Note: This analysis was conducted in visit 4 participants with a diagnosis of diabetes by visit 4.

Abbreviation: CI, confidence interval.

Model 1: Results adjusted for age, sex, race/study center.

Model 2: Results adjusted for Model 1 + low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, body mass index, estimated glomerular filtration rate, hypertension, parental family history of diabetes, education, smoking status, alcohol use, diuretic use.

Model 3: Results adjusted for Model 2 + fasting glucose + fasting insulin.

Web Table 5. Within-person change in uric acid concentration (mg/dL) in participants with diabetes at both visit 1 and visit 4 compared to participants without diabetes at both visit 1 and visit 4 (_n_ = 1,510)

	β (95% CI)	_P_ Value
Model 1	-0.46 (-0.56, -0.35)	<0.001
Model 2	-0.51 (-0.61, -0.40)	<0.001
Model 3	-0.27 (-0.42, -0.12)	0.001

Abbreviation: CI, confidence interval.

Model 1: Results adjusted for age, sex, race/study center.

Model 2: Results adjusted for Model 1 + low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, body mass index, estimated glomerular filtration rate, hypertension, parental family history of diabetes, education, smoking status, alcohol use, diuretic use.

Model 3: Results adjusted for Model 2 + fasting glucose + fasting insulin.

Web Figure 1. Study Design

Visit-based Incident Diabetes Cases
between Visits 1 and Visit 4
($n = 1,294$)

Visit 1 **Uric Acid** **Assessment** **1987-1989**	**Visit 4** **Uric Acid** **Assessment** **1996-1998**

Change in Serum Uric Acid

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Diabetes Duration: Time after
Diabetes Diagnosis (Including
Prevalent Cases) and before Visit 4
Uric Acid Measurement

Incident and
Prevalent
Diabetes Cases